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The Synthesis of Waltherione F and Its Analogues with Modifications at the 2- and 3-Positions as Potential Antitrypanosomal Agents

Victor Zdorichenko,[a] Romain Paumier,[a] Thomas Whitmarsh-Everiss,[a] Mark Roe[a] and Brian Cox*[a]

Abstract: Chagas disease also know as American Trypanosomiasis (AT) is a tropical parasitic disease endemic in South America, is caused by *Trypanosoma cruzi* which is transmitted by the blood-sucking insect vectors called triatomine bugs. Quinoline alkaloids from the root extract of *Waltheria indica* are known to possess antitrypanosomal activity. Waltherione F **3**, one of those alkaloids, was synthesised in 5 steps in 11% overall yield. We report here the first X-ray crystallographic confirmation of the structure of Waltherione F **3**. A key step in the sequence utilised the Conrad-Limpach synthesis for the formation of the quinolin-4(1*H*)-one ring system. Our synthetic strategy was designed to enable the modification of the 2- and 3-positions of the scaffold, allowing the generation of a diverse library of analogues to support our on-going medicinal chemistry program that is looking for new agents to tackle this devastating disease.

Introduction

Recently, Cretton *et al* reported the isolation of waltherione F **3**, a quinoline alkaloid, from the root extract of *Waltheria indica,*[1] along with waltheriones E – L (**2** – **9**) and 8-deoxoantidesmone **1** and antidesmone **10**; the latter two had already been described in the literature (Figure 1).[2]

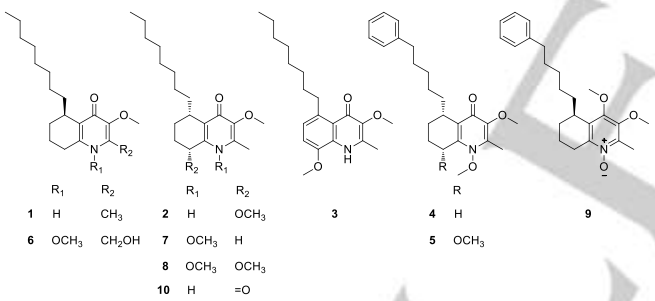


Figure 1. Alkaloids isolated from the dichloromethane extract of the roots of *Waltheria indica*.

The authors investigated the potential antitrypanosomal properties of the alkaloids, with compounds demonstrating activity against *Trypanosoma cruzi*, a parasite responsible for American Trypanosomiasis (AT), also known as Chagas disease, which is endemic in South America. The compounds were shown to selectively inhibit growth with IC_{50} values between 0.02 and 3.1 μM, which makes them a good starting point for a drug discovery program.

The synthesis of the oxabicyclic core of two structurally diverse waltheriones C **11** and D **12** has also been reported.[3]

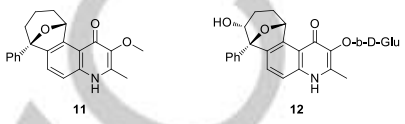
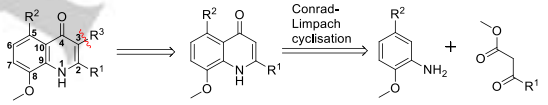


Figure 2. Waltheriones C and D (**11** – **12**).

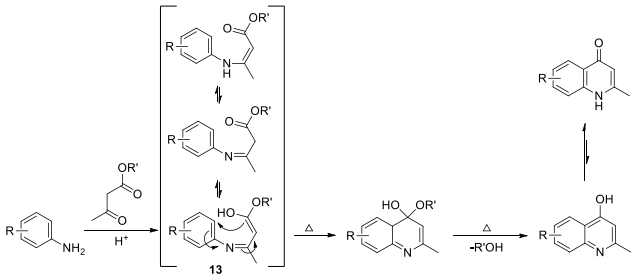
Results and Discussion

Here we report a total synthesis of waltherione F **3**. The molecule is accessible by a variety of synthetic methods available to make quinolines.[4] The key step in our strategy was the Conrad-Limpach synthesis of quinolin-4(1*H*)-ones which allowed the construction of the core, involving a reaction of an arylamine and a β-keto ester (Scheme 1).[5]



Scheme 1. Retrosynthetic plan for the total synthesis of waltherione F **3** and its analogues.

Traditionally solvents with very high boiling points are used for this reaction, because the substrate for the cyclisation must be in the high-energy imine-enol tautomer **13**, and because the cyclisation into the hemiketal breaks the aromaticity of the phenyl ring (Scheme 2).[6] Alternatively, a ketene–imine intermediate formed via direct elimination of the corresponding alcohol (R'OH) from the imine ester is an alternative reaction pathway. The cyclisation of this intermediate would also require the breaking of aromaticity and necessitate the same high-temperature solvents. Indeed, mineral oil and diphenyl ether are among the most used solvents.



Scheme 2. Mechanism of Conrad-Limpach synthesis of 4-hydroxyquinolines/ quinolin-4(1*H*)-ones.

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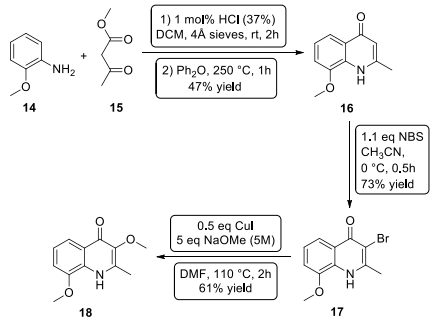
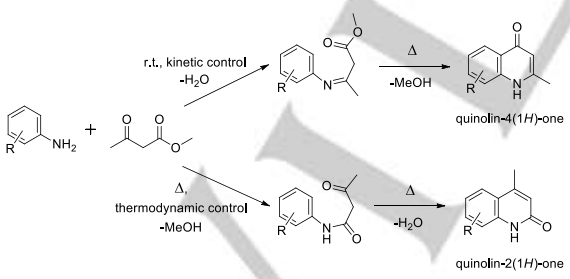
We set about designing a synthetic strategy around the Conrad-Limpach cyclisation that could be used for the total synthesis of the natural product but also that would be applicable to the synthesis of muliple analogues with modifications at the 2- and 3-positions to support our medicinal chemistry program. Our initial studies focused on the construction of the "core" of waltherione F **3** (Scheme 3) in order to investigate the manipulation of the 3-position.



Scheme 3. Investigation of the 3-postion of waltherione F **3**.

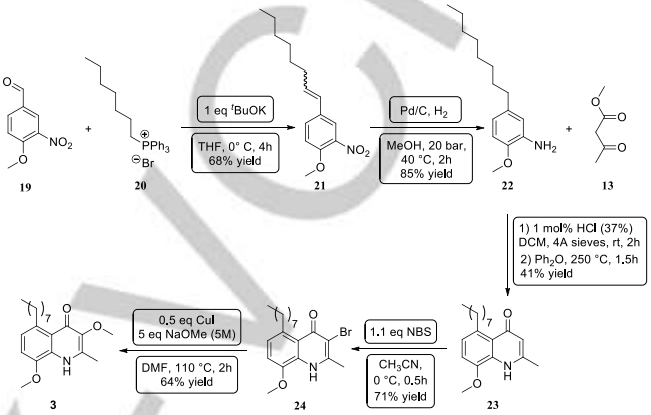
Following the Conrad-Limpach reaction protocol, reaction of 2-methoxyaniline **14** with methyl acetoacetate **15** afforded desired quinolone derivative **16**. It is important to acknowledge that the Conrad-Limpach synthesis can yield two structurally different isomers. During the condensation of an aromatic amine with a β-ketoester, the former can react either at a ketone or an ester group. If reaction happens at the ketone, the product is a quinolin-4(1*H*)-one; if the amine reacts at the ester, a quinolin-2(1*H*)-one is afforded. This reaction is often named Knorr quinoline synthesis, after Ludwig Knorr who reported in 1886 that modification of the reaction conditions yielded a quinolin-2(1*H*)-one.[7] Specifically, the reaction of the aromatic amine with the ketone group of the β-ketoester is *kinetically* favoured while nucleophilic attack at the ester group is *thermodynamically* favourable (Scheme 4).[8]



Scheme 4. Two possible products of the Conrad-Limpach synthesis.

Treatment of **16** with *N*-bromosuccinimide afforded 3-bromo-8-methoxy-2-methylquinolin-4(1*H*)-one **17**. Subsequent reaction with sodium methoxide catalysed by copper (I) iodide afforded 3,8-dimethoxy-2-methylquinolin-4(1*H*)-one **18**.

Having established that the 3-position could be easily modified post cyclisation, the total synthesis of waltherione F **3** was initiated. Commercially available 4-methoxy-3-nitrobenzaldehyde **19** was converted to 2-methoxy-5-octylaniline **22** *via* a Wittig reaction and subsequent hydrogenation, followed by cyclisation, afforded key intermediate 8-Methoxy-2-methyl-5-octylquinolin-4(1*H*)-one **23** (Scheme 5). Finally, bromination and methoxylation afforded the desired product in 11% overall yield.



Scheme 5. Waltherione F **3** synthesis.

Structures of **23** and waltherione F **3** were confirmed by X-ray crystallography (Figure 3).

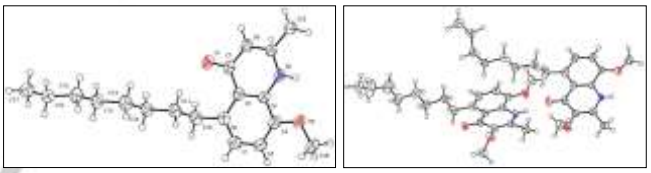


Figure 3. X-ray crystallography of **23** [left] and waltherione F **3** [right].

Having successfully synthesised waltherione F **3**, we turned our attention to the synthesis of analogues. A two-dimensional array of compounds was prepared varying the 2-position by the choice of β-keto ester in the Conrad-Limpach synthesis and varying the 3-position with the application of a number of different methodologies (Figure 4).

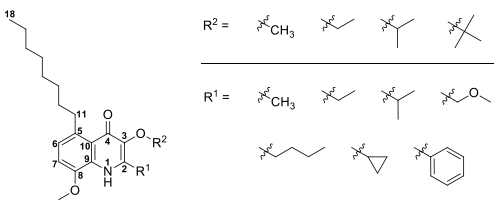
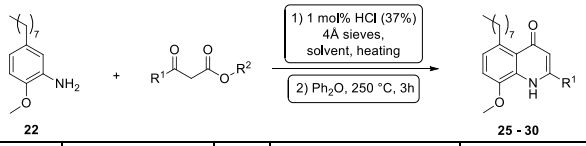


Figure 4. Analogues of waltherione F **3** chosen for synthesis.

Using the conditions for quinolin-4(1*H*)-one synthesis previously described in scheme 5, a series of β-keto esters were submitted for reaction with aniline **22** (Table 1).

Table 1. Attempted Conrad-Limpach syntheses of quinolin-4(1*H*)-ones **25 – 30** with reaction conditions for the first step of enamine formation and final cyclised product yield.



22 25 - 30

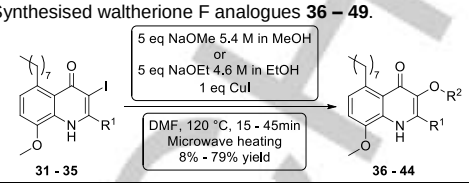
Product	R1	R2	Conditions for the intermediate enamine formation	Cyclised product yield (%)
25	Ethyl	Et	DCM, 16 h, 30 °C	52
26	Isopropyl	Et	DCM, 48 h, reflux	12
27	Methoxymethyl	Me	DCM, 36 h, reflux	48
28	n-Butyl	Me	DCM, 18 h, reflux	Mixture
		Me	n-Hexane, 24 h, reflux	56
29	Cyclopropyl	Et	DCM, > 18 h, reflux	0
30	Phenyl	Et	DCM, > 18 h, reflux	0

Cyclisation yields of compounds **25, 27, 28** were found to be moderate, ranging from 48% to 56%. Intermediate enamine formation proceeded very slow at room temperature, therefore reflux was performed in majority of the reactions. Slow rate and poor yields could perhaps be attributed to steric effects, further supported by the unsuccessful reactions of cyclopropyl and phenyl β-keto ester derivatives for which no evidence of enamine formation was observed after the stated reaction times. The crude intermediates were submitted for the cyclisation step in diphenyl ether but products **29**, **30** were not obtained, only aniline **22** starting material was recovered.

The total synthesis of waltherione F **3** utilised *N*-bromosuccinimide (NBS) reagent to selectively brominate the quinolin-4(1*H*)-one core at 3-position. With the aim of improving the subsequent Ullmann etherification, iodination using *N*-iodosuccinimide (NIS) was attempted. Compared to the carbon-bromine bond the carbon-iodine has a lower bond enthalpy, measured experimentally for the aryl halide C_6H_5X as 84 kcal mol^{-1} and 67 kcal mol^{-1} for X = 'Br' and 'I' respectively.[9] Therefore, we hypothesised that 3-iodoquinolin-4(1*H*)-ones should show an increased reactivity towards oxidative addition in the Ullmann condensation compared to 3-bromoquinolin-4(1*H*)-ones.

Attempts to optimise the alkoxylation of the 3-iodoquinolin-4(1*H*)-ones established that temperatures of 120 °C were required for an efficient conversion to the product and that using more than one equivalent of copper (I) iodide facilitated the undesired reductive dehalogenation process. Using a set of general conditions methoxylation and ethoxylation of 3-iodoquinolin-4(1*H*)-ones **31 – 35** were carried out successfully, yielding the waltherione F **3** analogues **36 – 43** (Table 2).

Table 2. Synthesised waltherione F analogues **36 – 49**.



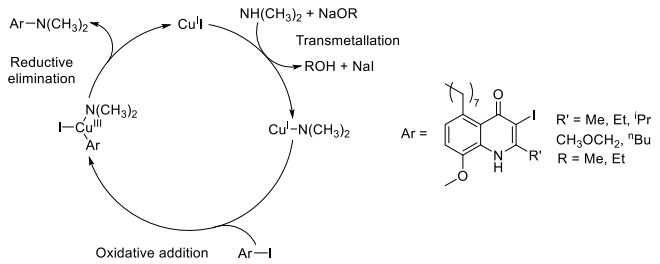
31 - 35 36 - 44

Product	R1 and R2	Yield %	By-product	Yield %
36	R^1 = Ethyl R^2 = Methyl	79	45	3
37	R^1 = Ethyl R^2 = Ethyl	52		
38	R^1 = Isopropyl R^2 = Methyl	76	46	5
39	R^1 = Isopropyl R^2 = Ethyl	41		
40	R^1 = n-Butyl R^2 = Methyl	36	47	13
41	R^1 = n-Butyl R^2 = Ethyl	25		
42	R^1 = Methoxymethyl R^2 = Methyl	8	48	20
43	R^1 = Methoxymethyl R^2 = Ethyl	12		
44	R^1 = Methyl R^2 = Ethyl	49	49	9

Waltherione analogues **36 – 43** were obtained in variable yields and deemed to be of sufficient purity by HRMS, ^1H and ^{13}C NMR analysis. Yields for methoxylation reactions were in general

greater than those for ethoxylation reactions, with ethoxylation reactions yielding a greater proportion of the reductive dehalogenation by-product. Methoxymethyl analogues **42** and **43** had significantly lower yields as they were observed to stick to the column during purification.

During the isolation of waltherione F **3** analogues, 3-dimethylaminequinolin-4(1*H*)-one species **45 – 49** were observed. It is well known that under basic conditions and elevated temperatures, such as those employed in the alkoxylation of the 3-iodoquinolin-4(1*H*)-one cores, DMF can be hydrolysed to produce dimethylamine which acts as a nucleophile in the Ullmann condensation (Scheme 6). [10],[11]



Scheme 6. Proposed mechanism for the Ullmann condensation with dimethylamine.

Attempts to synthesise waltherione F analogues in which R^2 = i-Pr and *t*-Bu using a variety of conditions with potassium *tert*-butoxide and sodium isopropoxide were unsuccessful. This observation could be due to unfavourable steric interactions.

A further modification at the 3-postion utilized the penultimate compound of the sequence towards Waltherione F **3**, 3-bromo-8-methoxy-2-methyl-5-octylquinolin-4(1*H*)-one **24**, in a microwave assisted palladium-catalysed Suzuki cross-coupling reaction to afford analogues **50** – **56**. Compound **24** was reacted with a range of boronic acids, the selection of which was guided by the work of Craig, where the aromatic substituents were chosen for their varying lipophilic and electronic properties (Table 3).[12]

Table 3. Synthesis of Waltherione F analogues **50 – 56**.

Product	R	Yield (%)
50	Phenyl	64
51	4-Chlorophenyl	55
52	3-Chlorophenyl	39
53	4-Methoxyphenyl	57
54	4-Tolyl	51
55	4-Cyanophenyl	42
56	4-Trifluoromethoxybenzyl	47

The authors would like to note that after completion of this work, a synthesis of waltherione F **3** using an alternative synthetic approach has appeared.[13]

Conclusions

Waltherione F **3** was synthesised in 5-step reaction sequence. One of the key reactions was the formation of 8-methoxy-2-methyl-5-octylquinolin-4(1*H*)-one **23** which was achieved within 6 hours which was an improvement of the 2 week synthesis reported in the literature for similar compounds.[14] Analytical data for synthetic waltherione F **3** correlated with that of natural material from the roots of *Waltheria indica* as reported by Cretton *et al*,[1] along with first X-ray crystallographic confirmation, thus successfully confirming the identity of waltherione F **3**.

A library of novel waltherione analogues **36 – 44** with variations at 2- and 3-positions were successfully synthesised utilising the Conrad-Limpach synthesis and Ullmann condensation. In synthesising analogues **36** – **44** the formation of what were later identified as 3-dimethylaminequinolin-4(1*H*)-one analogues **45 – 49** was observed and successfully isolated from their respective reaction mixtures.

A separate library of analogues **50** – **56** with varying aromatic and benzylic substituents at the 3-position was prepared using a microwave-assisted Suzuki cross-coupling reaction.

Work on the antitrypanosomal properties of the waltheriones is on-going and will be reported at a later date.

Experimental Section

For detailed experimental procedures, compound data and spectra see supplementary information.

2-Methoxy-5-octylaniline **22**

Heptyltriphenylphosphonium bromide **20** (2.40 g, 5.52 mmol) and anhydrous tetrahydrofuran (20 mL) were put in an oven dried 100 mL round-bottom flask and the mixture was left to cool to 0 °C in an ice bath. Potassium *tert*-butoxide (5.52 mL, 5.52 mmol) was then added dropwise to the reaction mixture which changed from colourless to a deep orange over a few seconds. After one hour, 4-methoxy-3-nitrobenzaldehyde **19** (1.00 g, 5.52 mmol) in anhydrous tetrahydrofuran (5 mL) was added to the reaction mixture, which quickly changed to a dark brown colour. After 4 hours, the reaction mixture was extracted with ethyl acetate (20 mL) and washed with water (3*10 mL). The organic phase was then dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude material was purified through flash column chromatography on silica gel (20% to 60% ethyl acetate in petroleum ether, R_f = 0.70) to afford a mixture of isomers **(*Z*)-21** and **(*E*)-21** as a yellow oil, which was subjected to the next step without further characterisation. (0.98 g, 3.75 mmol, 68% yield). 1-Methoxy-2-nitro-4-(oct-1-en-1-yl)benzene **(*Z*)/(*E*)-21** (0.98 g, 3.75 mmol) in methanol (10 mL) was run through a hydrogenation reactor at 20 bar and 40 °C with a palladium on carbon catalyst for 2 hours. The reaction mixture turned from yellow to orange over the course of the reaction. After the completion of the reaction, the mixture was concentrated under reduced pressure to afford orange oil. Subsequent physicochemical analysis confirmed this to be the title compound **22** (0.75 g, 3.20 mmol, 85% yield).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.70 (d, *J* = 8.0 Hz, 1H, ArH), 6.56 (d, *J* = 2.0 Hz, 1H, ArH), 6.53 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 3.82 (s, 3H, OCH_3), 3.72 (s, 2H, NH_2), 2.47 (t, *J* = 7.7 Hz, 2H, $ArCH_2R$), 1.56 (quint, *J* = 7.4 Hz, 2H, CH_2), 1.36 – 1.22 (m, 10H, aliphatic), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 145.7 (C=O), 136.0, 135.9, 118.3, 115.5, 110.6, 55.8, 35.5, 32.1, 31.8, 29.7, 29.5, 29.4, 22.8, 14.2; **MS (LCMS)** found *m/z* 236.1 $[M + H]^+$, R_t = 2.46 min; **HRMS (ESI)** exact mass calculated for $[C_{15}H_{26}NO]$ requires *m/z* 236.2009, found *m/z* 236.2010 $[M + H]^+$; **IR** (ν_{max}, cm^{-1}) 3418 (N-H stretch), 2961 (C-H stretch), 2920 (C-H stretch), 2851 (C-H stretch), 1515 (C=C bend, aromatic), 1228 (C-O stretch), 1027 (C-N stretch).

8-Methoxy-2-methyl-5-octylquinolin-4(1*H*)-one **23**

2-Methoxy-5-octylaniline **22** (0.40 g, 1.70 mmol), methyl acetoacetate **15** (0.20 g, 1.90 mmol), concentrated hydrochloric acid (0.10 mL, 0.02 mmol), anhydrous dichloromethane (30 mL) and activated 4Å molecular sieves were put in an oven-dried 100 mL round-bottom flask and left to stir under nitrogen atmosphere. The reaction mixture was left stirring for 4 hours which then was filtered and concentrated under reduced pressure affording a white amorphous solid. Diphenyl ether (10 mL) was put into a two-necked 50 mL round-bottom flask fitted with a Liebig condenser and a dropping funnel and the flask was heated to 250 °C. The intermediate was dissolved in diphenyl ether (10 mL) and added dropwise to the flask. The mixture turned from amber to dark brown over the course of the reaction. After 1.5 hours, the reaction mixture was cooled to room temperature and purified through flash column chromatography on silica gel (0% to 5% methanol in dichloromethane, R_f = 0.44) to afford a yellow solid. Subsequent physicochemical analysis confirmed this to be the title compound **23** (0.20 g, 0.68 mmol, 41% yield).

M.p. 116-119 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.58 (s, 1H, N-H), 7.05 (d, *J* = 8.1 Hz, 1H, ArH), 6.85 (d, *J* = 8.1 Hz, 1H, ArH), 5.82 (s, 1H, ArH), 3.93 (s, 3H, OCH_3), 3.16 (t, *J* = 7.6 Hz, 2H, $ArCH_2R$), 2.31 (s, 3H, $ArCH_3$), 1.46 (quint, *J* = 7.6 Hz, 2H, CH_2), 1.31 – 1.16 (m, 10H, aliphatic), 0.83 (t, *J* = 6.8 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 178.6 (C=O), 147.5, 146.2, 134.6, 132.4, 123.5, 122.7, 110.9, 110.3, 55.9, 34.1, 31.9, 31.2, 29.1, 28.9, 28.7, 22.0, 18.9, 13.8; **MS (LCMS)** found *m/z* 302.1 $[M + H]^+$, R_t = 2.51 min; **HRMS (ESI)** exact mass calculated for $[C_{19}H_{28}NO_2]$ requires *m/z* 302.2515, found *m/z* 302.2516 $[M + H]^+$; **IR** (ν_{max}, cm^{-1}) 2919 (C-H stretch), 2850 (C-H stretch), 1627 (C=O stretch), 1521 (C=C stretch, aromatic), 1730 (C-O stretch), 1170 (C-N stretch).

3-Bromo-8-methoxy-2-methyl-5-octylquinolin-4(1*H*)-one **24**

8-Methoxy-2-methyl-5-octylquinolin-4(1*H*)-one (0.10 g, 0.31 mmol) **23** in acetonitrile (8 mL) and *N*-bromosuccinimide (0.06 g, 0.35 mmol) in acetonitrile (5 mL) were put in a 25 mL round-bottom flask and left to stir at room temperature. Within a few seconds of the addition of *N*-bromosuccinimide, a white precipitate formed in the orange reaction mixture. After 2 hours, the reaction reached completion and the mixture was washed with water (3*10 mL), extracted with dichloromethane (10 mL), dried over magnesium sulphate and concentrated under reduced pressure to afford brown solid. Subsequent physicochemical analysis confirmed this to be the title compound **24** (0.08 g, 0.22 mmol, 71% yield).

M.p. 129-139 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.06 (s, 1H, N-H), 7.11 (d, *J* = 8.1 Hz, 1H, ArH), 6.95 (d, *J* = 8.1 Hz, 1H, ArH), 3.95 (s, 3H, OCH_3), 3.14 (t, *J* = 7.6 Hz, 2H, $ArCH_2R$), 2.59 (s, 3H, $ArCH_3$), 1.46 (quint, *J* = 7.6 Hz, 2H, CH_2), 1.33 – 1.16 (m, 10H, aliphatic), 0.83 (t, *J* = 6.6 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 172.0 (C=O), 146.9, 146.1, 134.5, 130.9, 124.7, 121.0, 110.6, 109.1, 56.0, 34.4, 31.8, 31.2, 29.1, 28.9, 28.7, 22.0, 20.8, 13.8; **MS (LCMS)** found *m/z* 380.0 $[M + H]^+$, R_t = 3.36 min; **HRMS (ESI)** exact mass calculated for $[C_{19}H_{27}BrNO_2]$ requires *m/z* 380.1220, found *m/z* 380.1227 $[M + H]^+$; **IR** (ν_{max}, cm^{-1}) 2921 (C-H stretch), 2851 (C-H stretch), 1622 (C=O stretch), 1559 (C=C stretch, aromatic), 1271 (C-O stretch), 1169 (C-N stretch).

3,8-Dimethoxy-2-methyl-5-octylquinolin-4(1*H*)-one **3** [1]

3-Bromo-8-methoxy-2-methyl-5-octylquinolin-4(1*H*)-one (0.08 g, 0.22 mmol) **24** in dimethyl formamide (5 mL), sodium methoxide (0.20 mL, 1.08 mmol) and copper iodide (0.02 g, 0.11 mmol) were put in a 50 mL round-bottom flask. The mixture was heated to 120 °C and then was left to stir and reflux for 2 hours. After reaction completion, the reaction mixture was filtered through a sintered funnel and the filtrate was concentrated under reduced pressure which afforded a yellow amorphous solid. The product was purified through flash column chromatography on silica gel (0% to 7% methanol in dichloromethane) to afford pale yellow solid. Subsequent physicochemical analysis confirmed this to be the title compound **3** (0.05 g, 0.14 mmol, 64% yield).

M.p. 108-110 °C; **^{1}H NMR** (500 MHz, Methanol-d_4) δ 6.98 (d, *J* = 8.1 Hz, 1H, ArH), 6.89 (d, *J* = 8.1 Hz, 1H, ArH), 3.97 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.25 (d, *J* = 7.7 Hz, 2H, $ArCH_2R$), 2.46 (s, 3H, $ArCH_3$), 1.58 (quint, *J* = 7.7 Hz, 2H, CH_2), 1.38 (p, *J* = 14.6, 6.8 Hz, 2H, CH_2), 1.34 – 1.21 (m, 8H, aliphatic), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3); **^{13}C NMR** (126 MHz, Methanol-d_4) δ 175.9 (C=O), 147.8, 143.2, 142.6, 136.8, 132.4, 125.3, 125.1, 110.6, 60.2, 56.6, 36.3, 33.6, 33.0, 30.9, 30.8, 30.5, 23.7, 14.4, 14.1; **MS (LCMS)** found *m/z* 332.1 $[M + H]^+$, R_t = 2.77 min; **HRMS (ESI)** exact mass calculated for $[C_{20}H_{30}NO_3]$ requires *m/z* 332.2220, found *m/z* 332.2223 $[M + H]^+$; **IR** (ν_{max}, cm^{-1}) 2920 (C-H stretch), 2850 (C-H stretch), 1629 (C=O stretch), 1518 (C=C stretch, aromatic), 1260 (C-O stretch), 1025 (C-N stretch).

2-Substituted quinolin-4(1*H*)-one derivatives **25 – 28**

1. To an oven dried round-bottom flask anhydrous dichloromethane, 2-methoxy-5-octylaniline **22** (1 equiv) and activated 4Å molecular sieves were added and left stirring under a nitrogen atmosphere. The β-Keto ester (1 equiv) was added dropwise to the stirred mixture before addition of 37% hydrochloric acid (0.01 equiv) and left stirring until completion for the indicated solvent, time and temperature. The reaction mixture was filtered through celite and the solvent removed under reduced pressure, yielding an intermediate. 2. Diphenyl ether (10 mL) was added to a three-necked round-bottom flask and fitted with a reflux condenser and dropping funnel before heating to 250 °C. The intermediate was added dropwise to the flask and the reaction left stirring for the indicated time, taking on a dark brown colour. The crude reaction mixture was left to cool to room temperature before purification using flash column chromatography on silica gel (100% dichloromethane followed by 0% - 7% methanol in dichloromethane), yielding the desired 2-substituted quinolin-4(1*H*)-ones **25** – **28**.

3-Iodo-quinolin-4(1*H*)-one derivatives **31 – 35**

To a 5 mL microwave vial, the quinolin-4(1*H*)-one core (1.0 equiv) was added and suspended in acetonitrile (5 mL) and cooled to 0 °C in an ice bath. To the stirred suspension, *N*-iodosuccinimide (1.1 equiv) was added and the reaction was brought to room temperature and left stirring for 1 hour. The solvent was removed under reduced pressure and the resulting solid dissolved in a mixture of dichloromethane (5 mL) and water (5 mL). The mixture was sonicated, filtered through a phase separation cartridge, and the organic phase was concentrated under reduced pressure, yielding the desired 3-iodoquinolin-4(1*H*)-ones **31 – 35**.

3-Alkoxy-quinolin-4(1*H*)-one derivatives **36 – 44**

In a 2 mL microwave vial, the 3-iodoquinolin-4(1*H*)-one core (1 equiv) and copper (I) iodide (1 equiv) were suspended in *N,N*-dimethylformamide (1 mL) before addition of the sodium alkoxide solution (5 equiv). The vial was heated in a microwave at 120 °C for the indicated time before reaching completion. The reaction mixture was filtered through a nylon filter and the solvent removed under reduced pressure. The crude solid was purified using a preparative HPLC system before filtering through a silica-supported carbonate cartridge, yielding the desired 3-methoxyquinolin-4(1*H*)-one and 3-ethoxyquinolin-4(1*H*)-one derivatives **36 – 44**.

3-Aryl- and 3-benzyl-quinolin-4(1*H*)-one derivatives **50 – 56**

A suspension of 3-bromo-8-methoxy-2-methyl-5-octylquinolin-4(1*H*)-one **24** (1 equiv), boronic acid (1.1 equiv) and bis(triphenylphosphine)palladium chloride (0.02 equiv) in acetonitrile (1 mL) was treated with aqueous 2M sodium carbonate (1 mL) and heated in a microwave at 100 °C for the indicated time before reaching completion. The reaction mixture was filtered through a nylon filter and the solvent removed under reduced pressure. The crude solid was purified using a preparative HPLC system before filtering through a silica-supported carbonate cartridge, yielding the desired 3-aryl- and 3-benzyl-quinolin-4(1*H*)-one derivatives **50 – 56**.

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Keywords: Waltherione F • Quinoline • Trypanosomiasis • Medicinal organic chemistry

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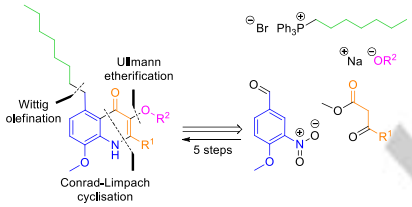

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